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(71) Applicant (for all designated States except US): **ASTELLAS PHARMA INC.** [JP/JP]; 3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8411 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **OHNISHI, Naozumi** [JP/JP]; c/o Astellas Pharma Inc., 3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo, 103-8411 (JP). **DEGUCHI, Shuhei** [JP/JP]; 3-5-30, Hayashi, Fuijidera-shi, Osaka 583-0007 (JP). **KITAMURA, Satoshi** [JP/JP]; c/o Astellas Pharma Inc., 3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo, 103-8411 (JP).

(74) Agents: **MORITA, Hiroshi** et al.; c/o Astellas Pharma Inc., 3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8411 (JP).

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(54) Title: NOVEL ORAL PHARMACEUTICAL SUSPENSION OF CEFDINIR CRYSTAL

(57) Abstract: The present invention relates to a novel oral pharmaceutical suspension of cefdinir crystal. More specifically, the present invention relates to a novel kit for preparation of an oral pharmaceutical suspension containing crystal form C Cefdinir.

DESCRIPTION

Novel oral pharmaceutical suspension of Cefdinir crystal

Technical Field

The present invention relates to a novel oral pharmaceutical suspension of crystalline Cefdinir. More specifically, the present invention relates to a novel kit for preparation of an oral pharmaceutical suspension containing crystal form C Cefdinir.

Background Art

7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer), known as Cefdinir, is a cephalosporin antibiotic having high antibiotic activity and broad antibacterial spectrum. Cefdinir was first disclosed in US 4,559,334, which is incorporated herein by reference.

To date, two crystal forms of Cefdinir have been observed and prepared in view of suitability for a pharmaceutical product and ease for handling. One crystal form of Cefdinir (hereinafter referred to as "crystal form A") has been disclosed in, for example, US 4,935,507, incorporated herein by reference, which has been widely used as an oral pharmaceutical suspension form.

Another crystal form of Cefdinir (monohydrate, also referred to as "crystal form B") including its method of preparation has been disclosed in JP Patent application No. 62-206199 found in the file of EP0304019, which is incorporated herein by reference. Recently, crystal form B has also been described in US 2003/0204082 A1. However, crystal form B of Cefdinir has not been used to form oral suspensions.

Summary of the Invention

In the present application, the present inventors have studied the physicochemical properties of the lower hydrates of Cefdinir, and established the present invention based on the novel knowledge gained from these studies.

Specifically, the present inventors have found that crystal form A of Cefdinir exists in an aggregate of small crystals, whereas the lower hydrates of Cefdinir, such as the monohydrate sometimes called crystal form B, exist in the shape of needles. Furthermore, the present inventors have found that the lower hydrates of Cefdinir transform to another hydrate having 1.5 to two or more waters of hydration per mole of Cefdinir in high moisture condition or aqueous solvent and exist as another crystal form, a higher hydrate. That is, in high moisture condition or aqueous media, the lower hydrates of Cefdinir transform to a higher hydrate (also referred to as "crystal form C") which may be present as the sesquihydrate, dihydrate, trihydrate, trihemihydrate, tetrahydrate, etc. or mixtures thereof. The term Crystal form C is simply convenient nomenclature for the product which results when one or more Cefdinir lower hydrates are converted into one or more higher hydrates in the presence of moisture or aqueous media. The sedimentation rate of crystal form C in aqueous solvent is lower than that of crystal form A, and dispersibility of crystal form C in aqueous solvent is higher than that of crystal form A. This phenomenon is most likely due to the shape of the lower hydrate crystal and the transformation of the lower hydrate crystal to crystal form C in aqueous solvent. The above-described properties of the lower hydrate and form C found by the present inventors make it easier for people to take an oral pharmaceutical suspension containing Cefdinir and allow for long storage of an oral pharmaceutical suspension containing Cefdinir.

In one aspect, the invention provides a kit for preparation of an oral pharmaceutical suspension of crystal form C Cefdinir, wherein said kit comprises: (a) a composition comprising a lower hydrate of Cefdinir within a first container; and (b) a label or a written

material indicating that said composition is admixed with pharmaceutically acceptable aqueous carrier prior to administration, wherein said composition when admixed with said carrier forms an oral pharmaceutical suspension of crystal form C Cefdinir.

In other aspect, the present invention provides an oral pharmaceutical suspension comprising crystal form C Cefdinir and pharmaceutically acceptable aqueous carrier.

In other aspect, the present invention provides a method for preparing an oral pharmaceutical suspension comprising crystal form C Cefdinir, comprising admixing composition containing a lower hydrate of Cefdinir with a pharmaceutically acceptable aqueous carrier.

In other aspect, the present invention provides a crystal form C Cefdinir.

In other aspect, the present invention provides a pharmaceutical composition comprising crystal form C Cefdinir.

Brief description of the drawings

Fig. 1 shows SEM micrographs of crystal form A and the monohydrate of Cefdinir.

Fig. 2 shows moisture adsorption / desorption isotherm at 25 °C of Cefdinir monohydrate.

Fig. 3 shows powder X-ray diffraction pattern of Cefdinir monohydrate at various relative humidities.

Fig. 4 shows powder X-ray diffraction pattern of Cefdinir monohydrate after stirring in water for 5 minutes.

Fig. 5 shows dispersion state of crystal form A of Cefdinir and Cefdinir monohydrate.

Fig. 6 shows change of transmittance of suspensions prepared with crystal form A of Cefdinir and Cefdinir monohydrate.

Detailed description of the present invention

The process for preparing Cefdinir is known in the art and has been disclosed in US 4,559,334, incorporated herein.

One process for preparing Cefdinir monohydrate is known in the art and disclosed in JP Patent application No. 62-206199. Another process has been disclosed in US 2003/0204082 A1. The monohydrate obtained may contain some crystal form A.

The term "lower hydrates" includes all hydrated forms of Cefdinir which convert in the presence of water or water moisture into higher hydrates (crystal form C) such as the sesquihydrate and trihemihydrate. One particularly preferred lower hydrate is the monohydrate, sometimes called crystal form B. Lower hydrates may contain up to about 1.25 moles of water per mole of Cefdinir. There is no minimum amount of water which the lower hydrates must contain except that it must be greater than zero. Generally, the lower hydrates will contain from about 0.5 to 1.25 moles of water per mole of Cefdinir, preferably about 1.0. The lower hydrates may contain a mixture of hydrated forms and also may contain some form A, from 0 to 50% by weight.

In one embodiment, the kit of the present invention comprises a composition comprising Cefdinir lower hydrate within a first container and a label or a written material indicating that said composition is admixed with pharmaceutically acceptable aqueous carrier prior to administration, wherein said composition when admixed with said carrier forms an oral pharmaceutical suspension of crystal form C Cefdinir. Preferably, the lower hydrate is the monohydrate. However, so far as oral suspension containing crystal form C Cefdinir can be formed, other crystal form than the lower hydrates of Cefdinir may be used in the composition. Crystal form C in the oral suspension includes any higher hydrate form such as sesquihydrate, dihydrate, trihydrate, trihemihydrate and tetrahydrate, so far as it is

converted from the lower hydrate in the oral suspension. Examples of the oral suspension of the present invention includes, but are not limited to, the oral suspension which mainly contains Cefdinir trihemihydrate containing 3.5 moles of water per mole of Cefdinir. The crystal lattice structure of trihemihydrate contains about 14 moles of water per the unit cell. About 10 moles of water are found in the crystal channels. However, the oral suspension may contain some other higher hydrates of Cefdinir such as sesquihydrate, dihydrate, trihydrate and tetrahydrate.

In one embodiment, the kit further comprises pharmaceutically acceptable aqueous carrier within a second container, wherein said carrier is admixed with said composition to form an oral pharmaceutical suspension of said crystal form C. In another embodiment, the kit further comprises a container used for admixing said composition with said pharmaceutically acceptable aqueous carrier to form an oral pharmaceutical suspension of said crystal form C.

Preferably, said composition comprising Cefdinir lower hydrate is admixed with said pharmaceutically acceptable aqueous carrier to form an oral pharmaceutical suspension of said crystal form C immediately before said oral pharmaceutical suspension is used. Alternatively, multiple doses of said composition comprising Cefdinir lower hydrate may be admixed with said pharmaceutically acceptable aqueous carrier at once and may be preserved for using at a later time.

The oral pharmaceutical suspension of the present invention comprises crystal form C Cefdinir and pharmaceutically acceptable aqueous carrier. The oral pharmaceutical suspension of the present invention can be prepared by admixing Cefdinir lower hydrate with pharmaceutically acceptable aqueous carriers.

The pharmaceutically acceptable aqueous carrier to be used in the present invention includes water and other diluent known in the art suitable for preparing oral pharmaceutical suspension. Preferably, the pharmaceutically acceptable aqueous carrier is water.

The oral pharmaceutical suspension of the present invention may include, if necessary, pharmaceutically acceptable additives including auxiliary substances, stabilizing agents, suspending agents, surface tension modifiers, viscosity modifiers, colorants, preservatives, flavoring agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, sucrose, and the like. In one embodiment, such additive may be included in the composition comprising Cefdinir lower hydrate in the kit of the present invention, and in other embodiment, such additive may be included in the pharmaceutically acceptable aqueous carrier in the kit of the present invention. In one embodiment, the composition comprised in the kit of the present invention contains about 125 mg of a Cefdinir lower hydrate and about 3.0 g sucrose, and the composition can be admixed with 5ml water as a pharmaceutically acceptable carrier to form an oral pharmaceutical suspension of crystal form C Cefdinir.

The container to be used in the present invention includes, but is not limited, bottle, vial, paper bag, test tube, and pharmaceutically acceptable container known in the art. The container may be formed from one or more materials such as plastic, glass or paper.

The amount of Cefdinir to be contained in the oral pharmaceutical suspension of the present invention may vary and depend upon the age, conditions of the patient, a kind of diseases, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. For example, an average single dose of about 10 - 1,000 mg, preferably about 50 - 500 mg, more preferably about 100 - 250 mg of Cefdinir may be used in treating diseases infected by pathogenic microorganisms.

Example

The monohydrate was prepared as follows: Cefdinir (20.0 g) was added to water (200 ml) and the mixture was adjusted to pH 6.0 with saturated sodium bicarbonate aqueous solution. The resultant solution was subjected to a column chromatography on activated charcoal and eluted with 20% aqueous acetone. Fractions were combined and then concentrated to 200 ml. This solution was adjusted to pH 2.2 at 15 °C with 10% hydrochloric acid and stirred at 0 °C for 30 minutes. The resultant crystals were collected by filtration, washed with water and dried to give crystals of Cefdinir monohydrate. The present inventors investigated physicochemical properties for Cefdinir monohydrate and crystal form A. The results are described below.

1. Scanning Electron Microscopy (SEM)

SEM micrographs (HITACHI S-800) of form A and the monohydrate are shown in Figure 1. It is clear from the figures that form A is an aggregate of small crystals, whereas the monohydrate is a needle shape.

2. Physical Properties

The present inventors investigate the interconversion of the forms as follows.

2-1. Moisture Adsorption / Desorption Isotherm

The moisture adsorption / desorption isotherms of the monohydrate were measured in relative humidities of 5 to 95% at 25 °C by microbalance method (VTI MB-300W (Microbalance) and MKA-510 (Kyoto electronics MFG, LTD.)). The obtained moisture adsorption / desorption isotherm is shown in Figure 2. The water increased to the content corresponding to higher hydrate form at the relative humidity of more than 70%, and to

trihydrate at the higher relative humidity such as 95%. To confirm the crystal form at each relative humidity, the powder X-ray diffraction (PXRD) patterns were measured at the each controlled relative humidity (10, 75, and 95% RH) (Rigaku RINT TTR2 and Rigaku HUMIDITY GENERATOR HUM-1). The obtained PXRD patterns are shown in Figure 3. It was confirmed that the obtained PXRD patterns were different from that of intact sample, that is, the PXRD pattern of the monohydrate measured at no controlled relative humidity. From these results, it was considered that the monohydrate transformed to another higher hydrate (crystal form C) at high relative humidity, and crystal form C keeps 1.5 or more molecules of crystalline waters.

2-2. Solvent medium Transformation

Form A and the monohydrate were suspended in water or ethanol (99.5) at room temperature, and the powder X-ray diffraction (PXRD) patterns of the residual solid materials were measured (Bruker AXS D8 Discover with GADDS). Figure 4 shows PXRD pattern of the residual solid obtained from the monohydrate after 5 minutes stirring in an aqueous suspension, and it was confirmed that the obtained pattern corresponded to that of another hydrate keeping much amount of molecules of crystalline water. Therefore, it was concluded that the crystalline change from monohydrate to crystal form C was occurred in an aqueous suspension.

On the other hand, form A showed no crystalline conversion to other crystal form in aqueous and ethanol suspensions.

3. Dispersibility comparison assay

The dispersibility of two crystal forms of Cefdinir was compared by evaluating sedimentation rates of two crystal forms. The evaluating sedimentation rate was conducted by using two methods as follow.

3-1. Method 1

About 1250 mg of crystal form A or the monohydrate were dispersed in 50 mL of water (125 mg/5 mL), and the suspensions were vigorously shaken by hand. Then, the appearances of contents were observed in a test tube (about sediments and lumps). The pictures of suspension states were taken with time. As shown in Figure 5, the dispersion state of the suspension of the monohydrate was better than that of form A, and the sedimentation rate of the monohydrate was slower than that of form A.

3-2. Method 2

5 mg of crystal form A or the monohydrate were dispersed in 10 mL of water (sample concentration: 0.5 mg/mL), and the suspensions were vigorously shaken. Then, the dispersed suspensions were transferred in the cell for UV measurement, and changes of the transmittances at 650 nm were measured. As shown in Figure 6, the transmittance of suspension prepared with form A showed the faster increase than that of the monohydrate, indicating that form A sank down faster than the monohydrate in the suspension. This result was corresponding to the observation result of dispersion rate.

The suspension properties of form A can be improved by grinding, however, this adds an additional step which is not necessary with the lower hydrates, such as the monohydrate.

CLAIMS

1. A kit for preparation of an oral pharmaceutical suspension of crystal form C of Cefdinir, wherein said kit comprises:

(a) a composition comprising Cefdinir within a first container; and

(b) a label or a written material indicating that said composition is admixed with pharmaceutically acceptable aqueous carrier prior to administration,

wherein said composition when admixed with said carrier forms an oral pharmaceutical suspension of crystal form C of Cefdinir.

2. A kit for preparation of an oral pharmaceutical suspension of crystal form C of Cefdinir, wherein said kit comprises:

(a) a composition comprising a lower hydrate of Cefdinir within a first container; and

(b) a label or a written material indicating that said composition is admixed with pharmaceutically acceptable aqueous carrier prior to administration,

wherein said composition when admixed with said carrier forms an oral pharmaceutical suspension of crystal form C of Cefdinir.

3. The kit of claim 2, wherein the lower hydrate of Cefdinir is monohydrate.

4. The kit of claim 1, 2, or 3, wherein said kit further comprises (c) pharmaceutically acceptable aqueous carrier within a second container.

5. The kit of claim 1, 2, or 3, wherein said kit further comprises (d) a container used for admixing said composition with said pharmaceutically acceptable carrier to form an oral pharmaceutical suspension of said crystal form C.

6. The kit of claim 1, 2, or 3, wherein the pharmaceutically acceptable carrier is water.

7. The kit of claim 1, wherein said Cefdinir is admixed with a pharmaceutically acceptable additive or mixture of additives.

8. The kit of claim 2, wherein the lower hydrate of Cefdinir is admixed with a pharmaceutically acceptable additive or mixture of additives.

9. An oral pharmaceutical suspension comprising crystal form C of Cefdinir, and a pharmaceutically acceptable aqueous carrier.

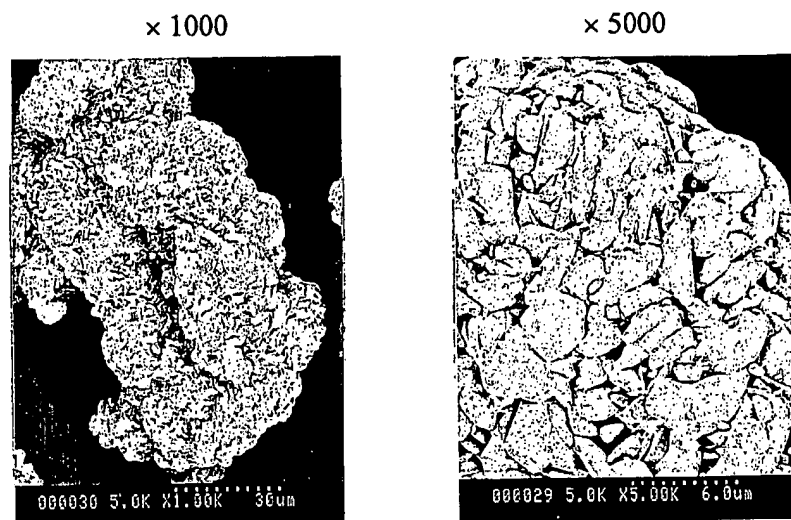
10. The oral pharmaceutical suspension of claim 9, wherein said suspension also comprises at least one pharmaceutically acceptable additive.

11. An method for preparing an oral pharmaceutical suspension comprising crystal form C of Cefdinir, comprising admixing composition containing the lower hydrate of Cefdinir with a pharmaceutically aqueous acceptable carrier.

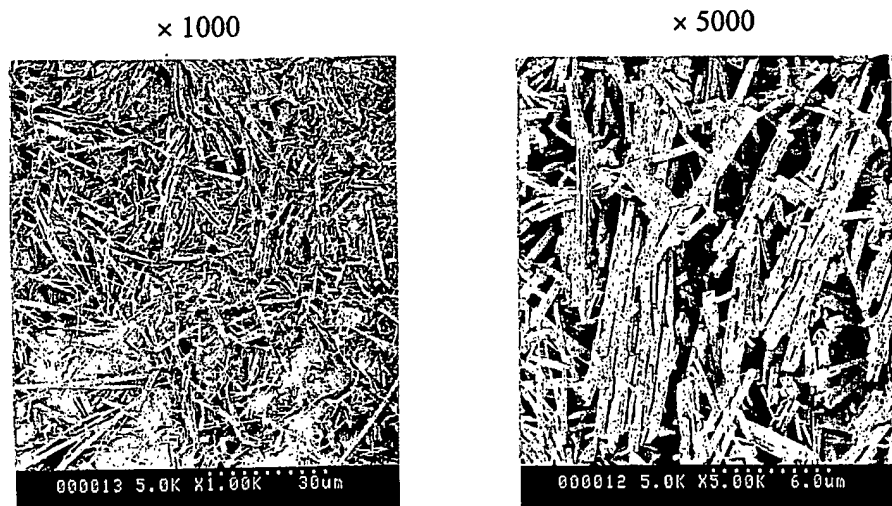
12. The method of claim 11, wherein the lower hydrate of Cefdinir is monohydrate.

13. A crystal form C of Cefdinir.

14. A pharmaceutical composition comprising crystal form C of Cefdinir.



Crystal form A



Monohydrate

Figure 1

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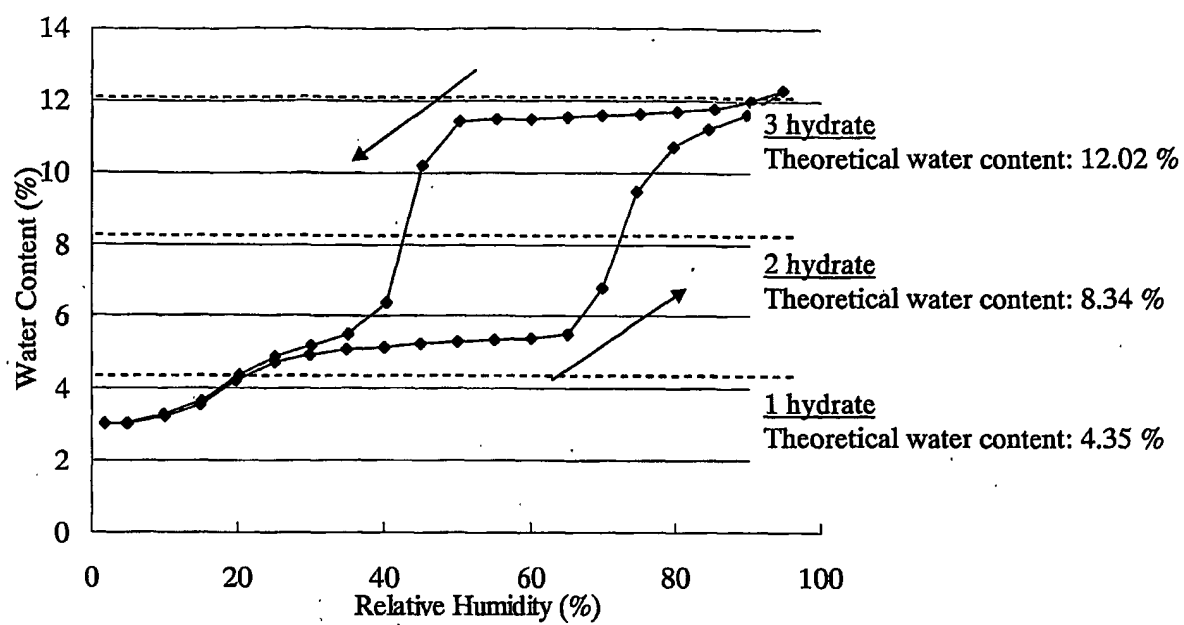
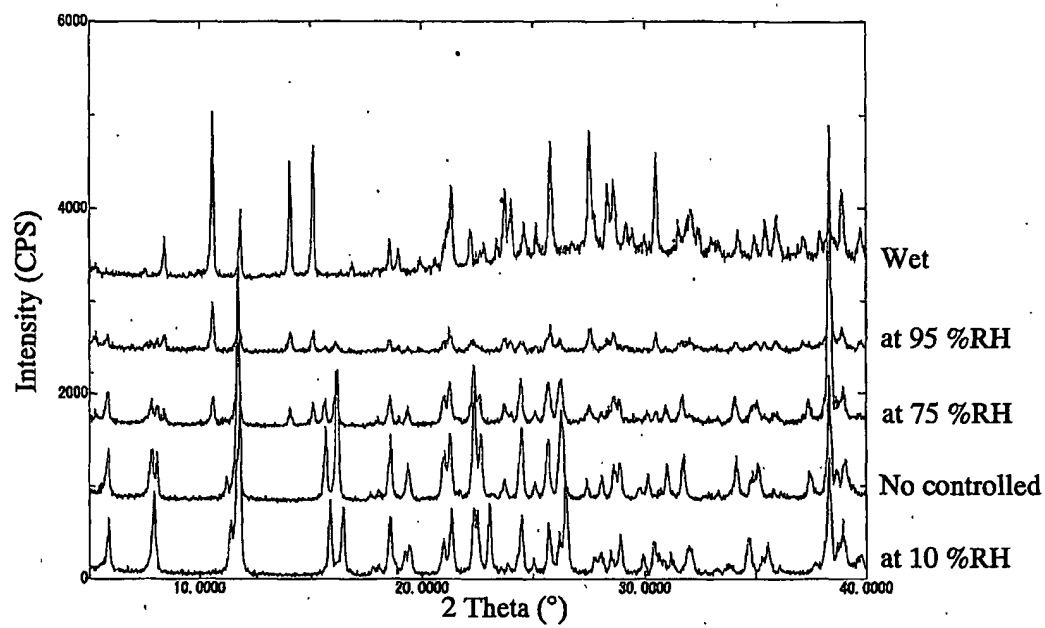


Figure 2

**Figure 3**

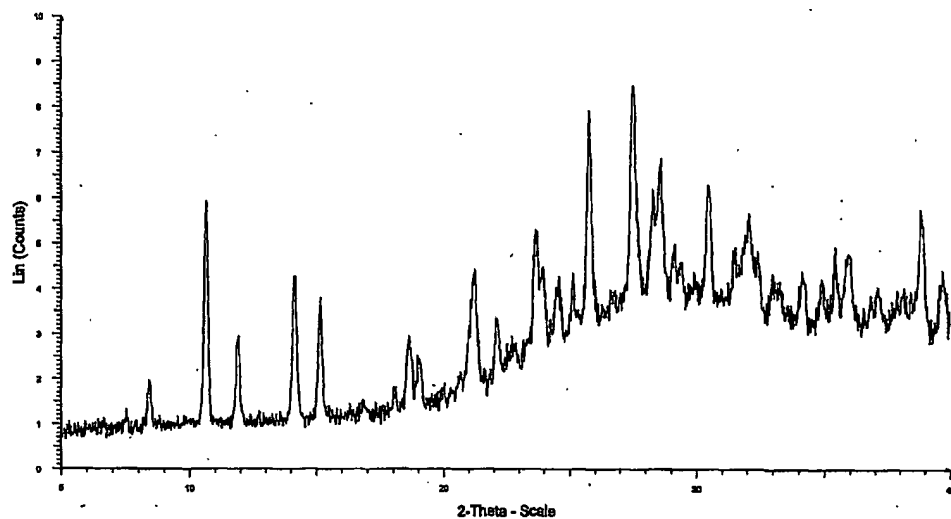
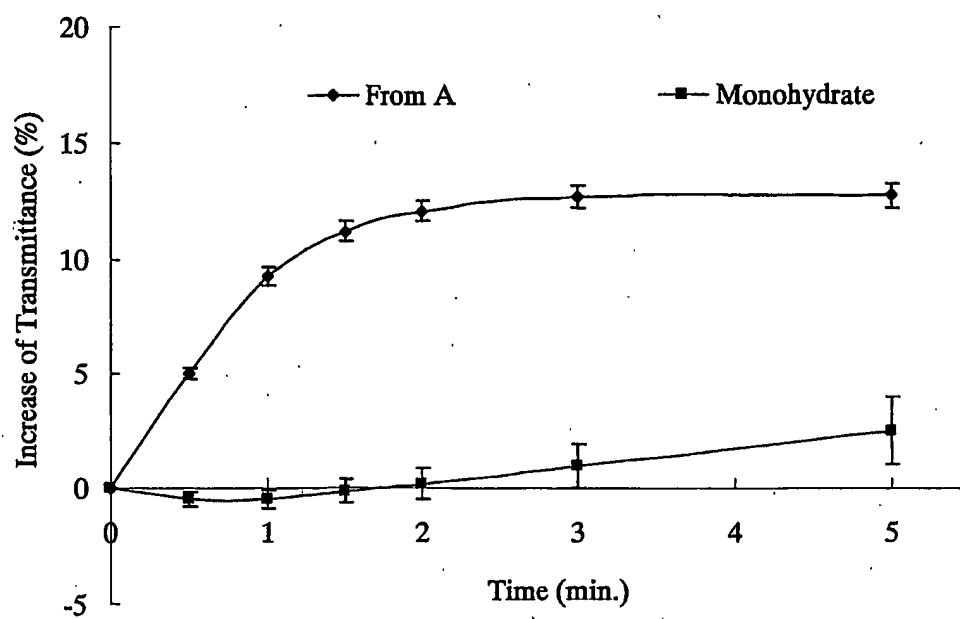


Figure 4



Figure 5

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**Figure 6**

INTERNATIONAL SEARCH REPORT

International application No
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| A. CLASSIFICATION OF SUBJECT MATTER A61K31/546 C07D501/22 A61K47/26 | | |
|---|---|--|
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | US 6 350 869 B1 (STURM HUBERT ET AL) 26 February 2002 (2002-02-26) example 2 | 1-14 |
| X | WO 03/050124 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; PRASAD, MOHAN; PRASAD,) 19 June 2003 (2003-06-19) example 4 | 1-14 |
| X | WO 2004/056835 A (ANTIBIOTICOS SPA [IT]; POZZI GIOVANNI [IT]; MARTIN GOMEZ PATRICIO [ES]) 8 July 2004 (2004-07-08) example 5 | 1-14 |
| A | US 2003/204082 A1 (MANCA ANTONIO ET AL) 30 October 2003 (2003-10-30) cited in the application the whole document | 1-14 |
| -/- | | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. | | |
| * Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "8" document member of the same patent family | | |
| Date of the actual completion of the international search 16 March 2006 | | Date of mailing of the international search report 27/03/2006 |
| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer Zimmer, B |

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2005/022249

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | "OMNICEF (CEFDINIR) CAPSULES - OMNICEF (CEFDINIR) FOR ORAL SUSPENSION" September 2000 (2000-09), XP002328280 Retrieved from the Internet: URL: http://web.archive.org/web/20010612122933/http://www.rxabbott.com/pdf [retrieved on 2005-05-17] the whole document | 1-14 |
| P,X | WO 2005/090361 A (ABBOTT LABORATORIES; LAW, DEVALINA; HENRY, RODGER, F; LOU, XIAOCHUN) 29 September 2005 (2005-09-29) the whole document | 1-14 |
| P,X | WO 2005/060936 A (ABBOTT LABORATORIES; PUJARA, CHETAN, P) 7 July 2005 (2005-07-07) claims | 1-14 |
| P,X | WO 2004/104010 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; PRASAD, MOHAN; PRASAD,) 2 December 2004 (2004-12-02) the whole document | 1-14 |
| P,X | US 2005/245738 A1 (SINGH GIRIJ P ET AL) 3 November 2005 (2005-11-03) the whole document | 1-14 |
| A | CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS" TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1998, pages 163-208, XP001156954 ISSN: 0340-1022 the whole document | 1-14 |

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2005/022249

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|-----------------------------|
| US 6350869 | B1 | 26-02-2002 | AT 405283 B 25-06-1999 |
| | | | AT 57097 A 15-11-1998 |
| | | | AU 731413 B2 29-03-2001 |
| | | | AU 7428898 A 30-10-1998 |
| | | | BR 9809745 A 20-06-2000 |
| | | | CA 2283718 A1 15-10-1998 |
| | | | CN 1251590 A 26-04-2000 |
| | | | DE 69816056 D1 07-08-2003 |
| | | | DE 69816056 T2 15-04-2004 |
| | | | WO 9845299 A1 15-10-1998 |
| | | | EP 0973779 A1 26-01-2000 |
| | | | HU 0002987 A2 28-02-2001 |
| | | | ID 22536 A 04-11-1999 |
| | | | JP 3421354 B2 30-06-2003 |
| | | | JP 2000514833 T 07-11-2000 |
| | | | NO 994466 A 15-09-1999 |
| | | | PL 335620 A1 08-05-2000 |
| | | | SK 134399 A3 16-05-2000 |
| | | | TR 9902406 T2 21-02-2000 |
| WO 03050124 | A | 19-06-2003 | AU 2002347539 A1 23-06-2003 |
| | | | CN 1617875 A 18-05-2005 |
| | | | EP 1458728 A1 22-09-2004 |
| | | | JP 2005516011 T 02-06-2005 |
| | | | US 2005080255 A1 14-04-2005 |
| WO 2004056835 | A | 08-07-2004 | AU 2003293746 A1 14-07-2004 |
| | | | EP 1572699 A1 14-09-2005 |
| US 2003204082 | A1 | 30-10-2003 | CA 2424501 A1 29-10-2003 |
| | | | JP 2004035543 A 05-02-2004 |
| | | | US 2005209451 A1 22-09-2005 |
| WO 2005090361 | A | 29-09-2005 | NONE |
| WO 2005060936 | A | 07-07-2005 | US 2005131079 A1 16-06-2005 |
| WO 2004104010 | A | 02-12-2004 | NONE |
| US 2005245738 | A1 | 03-11-2005 | NONE |